

Psychiatric comorbidity in patients with chronic daily headache and migraine: a selective overview including personality traits and suicide risk

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Abstract Studies on the prevalence and impact of psychiatric disorders among headache patients have yielded findings that have clarified the relationship between migraine and major affective disorders, anxiety, illicit drug abuse, nicotine dependence, and suicide attempts. Studies in both clinical and community-based settings have demonstrated an association between migraine and a number of specific psychiatric disorders. In large-scale population-based studies, persons with migraine are from 2.2 to 4.0 times more likely to have depression. In longitudinal studies, the evidence supports a bidirectional relationship between migraine and depression, with each disorder increasing the risk of the other disorder. Although a strong association has been demonstrated consistently for migraine and major depression, especially for migraine with aura,

there has been less systematic research on the links between migraine and bipolar disorder. This review will focus on the way in which psychiatric disorders decrease the quality of life and result in a worse prognosis, chronicity of the disease, and a worse response to treatment. Short-term pharmaceutical care intervention improves the patients' mental health, but it does not significantly change the number and severity of headaches. The increase in self-efficacy and mental health associated with pharmaceutical care may be instrumental in improving the long-term pharmacotherapy of patients with migraine and headache.

Keywords Psychiatric disorders · Headache · Suicide risk · Treatment

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Introduction

Chronic daily headache (CDH) refers to a group of disorders in which headache occurs 15 or more days per month for at least 3 months [1–5] and includes: chronic migraine (CM), migraine with or without aura and migraine aura without headache, chronic tension-type headache (CTTH), hemicrania continua (HC), and new daily persistent headache [6–8].

Chronic migraine (CM) affects 2.4% of the general population [5] and it is often comorbid with other conditions, such as depression (80%) [9], anxiety (70%) [9, 10], insomnia (71%) [11], chronic fatigue (66%) [12], and fibromyalgia (35%) [13]. Recently, studies have viewed the relationship between migraine and psychiatric disorder as (1) bi-directional [14] since migraine patients have a more than threefold risk of developing depression and (2) specific [15] since the presence of migraine increases a patient's risk of developing depression or panic attack

disorder and the presence of depression or panic attack disorder is associated with a greater risk of developing migraine.

Sheftel and Atlas [16], looking at clinical manifestations associated with daily chronic headache, found a high incidence of anhedonia, decreased concentration, decreased libido, decreased energy, and sleep disorders, all characteristic elements of depression. They proposed that headache is not simply a symptom of depression, but that headache and several mood and anxiety disorders are clinical entities that share some pathophysiological bases [15, 17–24], most likely disturbances in the serotonergic systems [20, 25–27].

Epidemiology

Epidemiological research has indicated an association between migraine and mood disorder with a lifetime prevalence of major depression three times higher among patients with migraine when compared with patients without migraine [28]. This comorbidity between CDH and psychiatric disorders seems to be more frequent in women, in chronic forms of migraine [29] and in first-degree relatives of patients with mood disorder and migraine [21]. Migraine with aura is strongly associated with an early age of onset of the mood disorder (OR 11.4, age < 15 years; OR 5.6, age 15–24 years) [20]. Migraine, weekly or daily, occurs in 3–15% of children [30, 31] while 9–33% of individuals suffer from non-migraine headache at least monthly [31]. The prevalence of migraine is highest among patients with bipolar II disorder (77%), and this is significantly different from the prevalence among bipolar I patients (14%) [32]. The unipolar group has a prevalence of 46%, in between the two bipolar groups [32]. This is in broad agreement with the study by Endicott [33], who found a 51% prevalence of migraine in patients with characteristics similar to bipolar II

patients. The results of some epidemiological studies are shown in Table 1.

Psychiatric disorders and headache

The presence of migraine or severe non-migraine headache increases a patient's risk of developing depression or panic attack disorder, whereas the presence of depression or panic attack disorder is associated with a greater risk of developing migraine, but not severe non-migraine headache [15]. Merikangas and colleagues [17], in a prospective study, supported the idea that anxiety induces or facilitates the onset of a primary headache, acting as trigger for the subsequent development of a mood disorder such as depression. People suffering from migraine were 12 times more likely to suffer from panic attacks [21] and 2.5 times more likely to suffer from depression.

Psychiatric comorbidity is more frequent in chronic pain syndromes, such as the chronic form of migraine [34]. It is important to distinguish between migraine with or without aura and aura without headache. In one population-based epidemiological study [17, 35], migraine with aura was associated with anxiety disorders, recurrent brief depression and hypomania, whereas only the phobic and panic disorders were more frequent among patients suffering from migraine without aura. Patients with tension-type headache did not differ from controls with respect to any of the affective or anxiety disorders. Oedegaard and colleagues [20] showed that a large number of patients presenting with major affective disorders have migraine aura without headache. These patients had a lower frequency of an affective temperament and a lower probability of having made a suicide attempt, as well as a higher age of onset of migraine auras relative to patients suffering from migraine with aura.

The more common psychiatric conditions related to migraine are depression, bipolar disorders, anxiety [(especially,

Table 1 Prevalence of migraine in bipolar disorder from previous studies

| Source | Method | Sample size | Migraine prevalence (%) |
|-----------------------------|---|------------------------|--|
| Blehar et al. (1998) | Medical section of DIGS | $N = 327$ $F = 186$ | Total 21.1 Females 26.5 |
| Cassidy and Flanagan (1957) | Self-report of headache | $N = 100$ | Total 49.0 |
| Mahmood et al. (1999) | Self-report of IHS migraine criteria | $N = 81$ $F = 37$ | Total 25.9 Females 27.0 |
| Marchesi et al. (1989) | Diagnosis by neurologist | $N = 30$ | Total 20.0 |
| Fasmer (2001) | Administered IHS migraine criteria | $N = 27$ | Bipolar I 13.0 Bipolar II 77.0 |
| Younes et al. (1986) | Mother's report of past diagnosis of migraine | $N = 21$ | Total 28.6 Females = 0 Male = 21 |

DIGS Diagnostic Interview for Genetic Studies, IHS International Headache Society

generalized anxiety disorders (GAD)] [17, 36] and somatoform disorders. These comorbid disorders have been identified in several epidemiological studies [22, 37–40] as well as in clinical studies of treatment-seeking patients [34, 40, 41]. The association between migraine and depression has also been studied in a number of large-scale community studies (Table 2).

The association of CDH with psychiatric disorders is controversial, especially with regard to depression (Table 3). Verri and colleagues [10] found an association between CDH and at least one psychiatric disorder in 90% of their patients, mainly GAD, followed by major depression (25%) and dysthymia (17%). Verri [10] and later Juang [48] confirmed that a longer major depressive disorder (or chronic depression) was the most frequent comorbidity among these patients, especially when the chronic headache had lasted for more than 5 years. However, Juang and colleagues [48] found that the frequency of any type of anxiety disorder was significantly higher in patients with chronic migraine than in those with CTTH. In prior research, the comorbidity between tension-

type headache and psychiatric disorders has been investigated only in clinical populations, in which it has been showed that this association is more common in the chronic form of tension-type headache [14]. In fact, the frequency of anxiety and mood disorders were 3–15 times higher in CTTH patients than in controls [14], and the frequencies reported were 21% for depression and 17% for anxiety disorders in these patients [41], with significantly higher anxiety and depression scores [41, 49]. Moreover, in previous studies, especially in the chronic form of tension-type headache, affective disorders were found to be frequent [50, 51]. Of the three studies conducted in clinical samples, none reported any significant differences in psychiatric comorbidity between migraine and tension-type headache [49, 52, 53].

There has been less research on the role of personality disorders in headache. Mathew [54] found significantly higher abnormal personality profiles in CDH patients than in controls using the Minnesota Multiphasic Personality Inventory (MMPI) but found no difference in the profiles of patients with different subtypes of CDH. In a small sample

Table 2 Select studies of the association between migraine and depression

| Study | Method | Migraine and depression OR (95% CI) | Bi-directional relationship OR (95% CI) |
|-------------------------|--------------------------|--|---|
| Longitudinal studies | | | |
| Breslau et al. [37] | IHS migraine criteria | Not assessed | New-onset migraine 3.5 (2.2–5.6) New-onset depression 3.6 (2.6–5.2) |
| Breslau et al. [15] | IHS migraine criteria | 3.5 (2.6–4.6) | New-onset migraine 2.8 (2.2–3.5) New-onset depression 2.4 (1.8–3.0) |
| Breslau et al. [42] | IHS migraine criteria | Not assessed | New-onset migraine 3.4 (1.4–8.7) New-onset depression 5.8 (2.7–12.3) |
| Cross-sectional studies | | | |
| Merikangas [43] | Diagnosis by neurologist | 2.2 (1.1–4.8) | Not assessed |
| Breslau et al. [15] | IHS migraine criteria | 3.5 (2.6–4.6) | New-onset migraine 2.8 (2.2–3.5) New-onset depression 2.4 (1.8–3.0) |
| Swartz [44] | IHS migraine criteria | 3.1 (2.0–4.4) | New-onset migraine 0.68 (0.02–2.0) |
| Zwart [45] | IHS migraine criteria | 2.7 (2.3–3.2) | Not assessed |
| McWilliams [46] | Diagnosis by neurologist | 2.8 (2.2–3.7) | Not assessed |
| Patel [47] | IHS migraine criteria | Strict migraine 2.7 (2.2–3.3) Probable migraine 1.9 (1.5–2.4) | Not assessed |

Table 3 Studies of psychiatric comorbidity in patients with chronic daily headache

| Study | Criteria for headache diagnosis | Criteria for psychiatric diagnosis | Mood disorders (%) | Anxiety disorders (%) |
|-----------------------------|---|-------------------------------------|--|--|
| Mathew et al. [54] | By their own criteria | MMPI subscore | 61 | Not assessed |
| Verri et al. [10] | IHS | DSM IIIR (SCID-P) | Major depressive disorder: 25 dysthymia: 17 | GAD: 69.3 |
| Puca et al. [34] | IHS | CIDI-by physicians | 45 | 56 |
| Mitsikostas and Thomas [49] | IHS + mixed type headache | Psychiatric evaluation if HDRS > 16 | 10 (10 in CTTH, 19 in MOH, 9 in mixed type) | Not assessed |
| Wang et al. [76] | Adopted criteria of Silberstein et al. [2] + IHS for CTTH | DSM IV (GDS-S) | 29 | Not assessed |
| Juang et al. [48] | Adopted criteria of Silberstein et al. [2] | DSM IV (MINI) | Major depressive disorder: 55 dysthymia: 11 | GAD: 5 Panic: 27 |
| Holroyd et al. [41] | IHS | BDI | Major depressive disorder: 21 | 17 |
| Atasoy et al. [75] | ICHD II | DSM IV (SCID-II, SCID-CV) | 37.3 (25 in Group C; 51.6 in Group E; 36.2 in Group M) | 15.3 (10.7 in Group C; 16.1 in Group E; 17.2 in Group M) |

MINI International Neuropsychiatric Interview; *SCID* the Structured Clinical Interview for DSM-IV; *GDS-S* Geriatric Depression Scale-short Form; *IHS* International Headache Society; *CTTH* Chronic Tension-type Headache; *MMPI* Minnesota Multiphasic Personality Inventory; *HDRS* Hamilton Depression Rating Scale; *GAD* Generalized Anxiety Disorder; *BDI* Beck Depression Inventory; *CIDI* Composite International Diagnostic Interview; *ICHD-II* The international classification of headache disorders, 2nd edition; *MOH* Medication-Overuse Headache

study, high MMPI scores have been reported for the hypochondriasis and hysteria scales in CDH patients [55].

Galli and colleagues noted that only 9.6% of patients did not have familial occurrence of headache, with a half of the sample (49%) showing both parents and grandparents complaining of headache. Galli et al. [56] stressed the importance of familial recurrence (mainly for the mother) for migraine and psychiatric disorders, but less so for tension-type headaches and psychiatric disorders. The tension-type headache group had higher temperament traits of emotionality and shyness, and lower sociability, than the migraine group [57]. A higher emotionality score was also found among the parents and siblings of tension-type headache children [57]. Thus, high scores for emotionality and shyness can be considered to be symptoms of ‘behavioral inhibition’ [58, 59], characterized by the traits of irritability, shyness, fearfulness, and introversion. In school-age children, the presence of this temperament seems to increase the vulnerability to depressive and multiple anxiety disorders [60, 61]. Tension-type headache patients may have, as a group, more behavioral, emotional, and temperament difficulties than children referred for migraine [56]. This finding seems to be in contrast with an epidemiological study in Finland, which found that psychiatric symptoms tended to be more strongly associated with migraine than with tension-type headache [62]. However, personality disorders are considered to be a complication for headache management [63–65], and significant headaches are a complaint of about 60% of patients with

personality disorders presenting for acute treatment at a hospital emergency department [65].

Suicide risk

Suicide attempts seem to be more frequent in patients suffering from migraine than in the general population, especially in females and in patients with migraine with aura. This association has also been found in the general population [22, 35, 43, 66]. In contrast, the subtypes of CDH, headache frequencies, or medication overuse were not correlated with the risk of attempted suicide [66].

Migraine with aura also independently predicted a high suicidal risk (score > 10 on the MINI Suicidality Module) in adolescents with CDH [66], despite the fact that it is very difficult to predict suicide in youths. A history of migraine with aura, but not migraine without aura, has been found to be associated with an increased frequency of suicidal ideation and suicide attempts in patients with major depression in several studies [22, 39, 66], both current and previous affective episodes [20, 28]. Oedegaard and colleagues found that only 17% of patients having migraine aura without headache had made a suicide attempt, and these patients has the lowest frequency of affective temperaments as well as a higher age of onset of migraine auras [28]. However, the frequencies of suicidal ideation were approximately equal in the two groups of migraine patients [28].

Breslau [39] found an association of migraine with aura with suicide attempts that was not necessarily due to coexisting major depression. Migraine with aura alone was associated with significantly higher rates of suicidal tendencies. The risk of suicidal inclinations associated with migraine with aura and major depressive disorder was much higher than that for those with only major depressive disorder [67]. CDH is a source of great distress, with impairment of pleasure and working activities. This decreased quality of life can result in hopelessness and despair, and suicidal wishes can easily emerge [67]. However, the pain of headaches is itself a potential independent risk factor for suicide, particularly among those with chronic headache or multiple sources of co-occurring pain [68]. Individuals suffering from chronic pain may be particularly appropriate for suicide screening and intervention efforts. Innamorati and colleagues [69] have proposed a new scale, the Italian Perceived Disability Scale, as screening tool to identify comorbidity with emotional distress and disorders. This scale has proved able to predict suicidal intent in CDH patients and to assess disability in a sample of patients with CDH [69].

Treatment

The use of psychoactive drugs can influence the frequency and modify the clinical features of migraine headaches. For acute treatment, sumatriptan, nonsteroidal anti-inflammatory agents, ergotamine, and dihydroergotamine have been used, and metoclopramide is often co-administered.

The SSRIs (paroxetine and fluvoxamine) remain the first-choice medications for mood disorders related to migraine, although long-term treatment with serotonergic compounds does not impact the migraine itself. The SSRIs can also be used for the long-term treatment of panic disorder without mood disorders, tension-type headache, obsessive-compulsive disorder and somatoform disorder [70]. Regarding GAD and tension-type headache, the administration of BZDs is possible, but long-term therapy with BZD is not feasible because of the development of tolerance. In GAD long term therapy, SSRI (paroxetine) could represent a valid alternative to BZD if starting with a minimal effective dosage. The aim is to customize treatment as much as possible. The association between migraine and panic disorder and bipolar disorder or unipolar disorder can be treated with VPA, which is effective in the control of panic [71].

For the preventive treatment of mood disorders related to migraine or tension-type headache, the recommended therapy is to use antidepressive tricyclics (TCAs) [72], such as amitriptyline, as monotherapy or a combination of amitriptyline and an SSRI such as paroxetine [16] or flunarizine [73] and mood stabilizers such as lithium [21] or valproate [73, 74]. These have been tested and found to be

Table 4 Preventive treatments in headache associated with depressive syndrome

| |
|--|
| Preventive treatment |
| Migraine + depression + anxious symptoms: antidepressants with sedative properties |
| TCAs: amitriptyline |
| SSRIs: paroxetine, fluvoxamine |
| SNRIs: mirtazepine |
| Migraine + depression with psychomotor slowing: antidepressants without sedative properties |
| SSRIs: fluoxetine |
| Inadvisable drugs |
| Flunarizine |
| Beta-blockers |

Table 5 Preventive treatments in headache associated with panic disorder

| |
|---|
| <i>Short-term treatment</i> |
| BZDs: alprazolam, clonazepam |
| <i>Long-term treatment</i> |
| Migraine + panic disorder: VPA |
| Migraine + panic disorder + bipolar disorder: VPA |
| Migraine + panic disorder + secondary depression: antidepressants with sedative properties |
| TCAs: amitriptyline |
| SSRIs: paroxetine, fluvoxamine |
| SNRIs: mirtazepine |
| Migraine + depression + secondary panic disorder |
| Prevalence of anxiety symptoms: antidepressants with sedative properties |
| TCAs: amitriptyline |
| SSRIs: paroxetine, fluvoxamine |
| SARI: trazodone |
| Prevalence of psychomotor slowing: antidepressants without sedative properties |
| SSRIs: fluoxetine |

VPA Valproate

useful for migraine prophylaxis. No studies have reported a positive effect of the SSRIs on the aura symptoms. The better strategies are summarized in Tables 4 and 5.

Although, short-term pharmaceutical care intervention improves patients' mental health, it does not significantly change the number and severity of headaches. However, the increase in self-efficacy and mental health associated with pharmaceutical care may be instrumental in improving the long-term pharmacotherapy of patients with migraine and headache.

Conclusion

Several studies have analyzed the prevalence and impact of psychiatric disorders among headache patients, and these

studies have resulted in a better understanding of the relationship between migraine and mood disorders, anxiety, and suicide attempts. Unfortunately, as noted by Silberstein et al. [2], the relationship between headache and psychopathology has often been discussed only clinically rather than systematically studied. Furthermore, the investigation of the interplay of factors that precipitate suicide risk should include the assessment of chronic headache and its effects on well-being. These issues, as well as those discussed in this paper, represent an important area for future research.

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Conflict of interest None.

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